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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,464	04/29/2002	Peter L. Oren	29342/36230A	6930

4743 7590 09/21/2005

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EXAMINER	
CHANNAVAJJALA, LAKSHMI SARADA	
ART UNIT	**PAPER NUMBER**
1615	

DATE MAILED: 09/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/031,464	OREN ET AL.	
	Examiner	Art Unit	
	Lakshmi S. Channavajjala	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-16,18-25 and 28-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-16,18-25 and 28-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7-11-05 has been entered.

Claims 1-4, 6-16, 18-25 and 28-36 are pending in the instant application.

Claim Rejections - 35 USC § 103

Claims 1-4, 6-16, 18-25 and 28-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/03675 (Daung) in view of WO 96/38131 (Butler) and US 4,721,709 to Seth et al (Seth).

Daung teaches the claimed beta-carboline compounds and compositions containing the compounds, as also acknowledged by applicants on page 2 of the instant application. Daung specifically discloses teaches instant preferred compound (instant specification, page 3, lines 28-30) for treating conditions where inhibition of PDE5 is beneficial (see page 3, lines 24-25, lines 30-32 and is also referred to as compound A). On page 12, lines 11-12, Daung teaches that the compounds a and B are prepared as different dosage forms and in particular, Table B shows a tablet prepared by wet granulation, where in the tablet composition contains beta-carboline drug as active agent and other excipients such as polyvinylpyrrolidone, PEG, Polysorbate 80,

magnesium stearate, crosscaramellose sodium, and microcrystalline cellulose, which read on the instant claimed binder, diluent, wetting agent, lubricant and disintegrant respectively. Instant dependent claims specifically recite the excipients of Table B of Daung. With respect to the percentages of active ingredients and the excipients claimed, the total weight of the composition of tablet in Table B is 500 mg. A calculation of the proportion of each ingredient in Table 2 reads on the instant claimed percentages. With respect to the claimed "free drug", Daung does not teach an intimately embedded drug in a polymeric co-precipitate and hence meets the definition of instant "free drug" (instant page 5, lines 24-27). Instead, Daung only teaches direct compression or wet granulation followed by compression to prepare the tablets (pages 12-14).

Daung fails to teach the claimed particulates and sizes of particles, exact or the percentages of diluent (claim 5), lubricant (claim 8), binder (claim 10), and the claimed amounts of drug in tablet (claims 22, 23) and capsule (claim 25). However as acknowledged by applicants, Daung teaches the active agent and also for the same purposes i.e., as a 5PDE inhibitor. Further Daung teaches the pharmaceutical compositions containing the same active compound and excipients, as claimed, in the form of tablets and capsules. Accordingly, optimizing the amounts of art recognized excipients such as binder, lubricant, optimizing the amount of active compound with an expectation to achieve the appropriate dosage form as well the desired therapeutic efficiency of the drug would have been within the scope of a skilled artisan because Daung suggests optimizing the amounts of drug in the range of 0.5 to 800 mg per day

and also employing the suitable excipients depending on the route of administration (page 5).

Butler teaches pharmaceutical compositions comprising beta-carboline compounds (abstract, page 4, lines 15-21). The specific beta-carboline compound taught by Butler is the same as that claimed in the instant invention. Further, Butler teaches that the above are poorly soluble in nature. Butler teaches solid dispersions but fails to teach the claimed particle sizes.

Seth teaches pharmaceutical composition containing poorly water-soluble drugs and a method of preparing the same. The method of Seth is practically applicable to all water insoluble drugs and comprises the steps of providing dry powder of the insoluble drug that is adsorbed on to a carrier such as starch or cellulose and is characterized in that the drug is present particulate form and at least 95% of the drug particles have a mean size of less than 15 microns (col. 4, lines 44-53, col. 3, lines 60-67), which is in the same range as claimed. Seth teaches that the drug particles are closely associated with the carrier and details the method of preparing the formulation in col. 6, lines 1-39. Further, Seth teaches preparation of various dosage forms such as tablets, capsules etc., with the above prepared formulation (col. 8). Examiner notes that instant specification refers to US patent 4,605,517 by incorporation for the preparation of the instant drug formulation. It is noted that the above patent also recites the same method of preparation as that of Seth. Therefore, it would have been obvious for one of an ordinary skill in the art at the time of the instant invention to prepare drug formulations of beta-carboline of Daung containing the excipients such as lubricants, wetting agents

etc., by the process of Seth i.e., particulate drug adsorbed on to excipients or carrier and compressing into tablets because Seth teaches that the conventional methods of jet milling or pin milling employed in drug preparation result in slow dissolution and absorption, (col. 2, lines 1-20) and that their method avoids the disadvantages of agglomeration and poor flow seen in the conventional methods. Accordingly, the expected result would be an increased dissolution of beta-carboline and hence increased bioavailability without agglomeration.

Double Patenting

Claims 1-4, 6-16, 18-25 and 28-37 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U. S. Patent No. 6,821,975. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claimed composition containing a free drug, beta-carboline together with excipients and also composition comprising particulate form of the drug is also claimed in the above patent applications. The patent claims a free drug particulate form of beta-carboline, compositions containing the free drug, a method of treating a patient in need thereof. The copending claims also recite particle sizes and broadly recite carriers or excipients, as in instant claims. While the patent fails to list the specific diluents and other excipients of the instant claims, choosing an appropriate solvents, diluents, and other

art recognized pharmaceutical excipients with an expectation to prepare a desired dosage form would have been obvious for one of an ordinary skill in the art.

Response to Arguments

Applicant's arguments filed 7-11-05 have been fully considered but they are not persuasive.

35 U.S.C. 103(a) REJECTION:

Applicants argue that instant composition exhibits unexpected and surprising results in therapeutic delivery of compound A through enhanced dosage uniformity, stability ad bioavailability and thus rapid onset of a therapeutic effect. This unexpected result, applicants state, is due to the compound A as a free drug, the particle size and the presence of ingredients such as water-soluble diluent, lubricant etc. Applicants argue that WO '675 fails to teach the above features. Applicants compared the difference between instant composition and that of WO '675 and argue that the PEG of the reference, by definition is not included in the list of "polyols" as suitable water-soluble diluent. However, instant claim 1 only recites a water-soluble diluent and does not exclude PEG of WO '675. Besides, PEG is defined as a water-soluble compound (see the definition of PEG, as given in Hawley's Condensed Chemical Dictionary, 1997, page 898). Applicants' argue that the amount of PEG in the reference is much lower in amounts than that claimed in the application. However, absent any unexpected results with respect to the high amounts of PEG, it is examiner's position that the optimizing the amount of a diluent so as to achieve the desired dilution would have been within the

scope of a skilled artisan. In response to the argument that the reference does not teach PVP, table 2 (on page 13) clearly describes PVP. While applicants argue that WO '675 is silent regarding the free form of a compound, examiner clearly explained, based on applicants own definition of "free base" that the reference meets the claim term. Further, the burden is shifted to applicants to establish that the compound is in fact not a free drug.

Applicants argue that WO '131 explains the problems associated with free forms of water-soluble drugs and overcomes the problem with co-precipitation. Therefore, applicants conclude that WO '131 teaches away from a free base of the drug. However, WO '131 nowhere compares and teaches away from preparing a free drug formulation as opposed to the preferred co-precipitate. The rejection clearly cites the teachings of WO '131 to show that the compounds claimed are known to be poorly soluble and not for the claimed particle sizes. '709 teach employing particulate material to improve dissolution and also avoid the problems of agglomeration and poor flow. Thus, the motivation to employ a particulate compound in the teachings of Daung comes from the teaching that the compounds are poorly soluble (WO '131) and that preparing fine particles of a poorly soluble drug improves the dissolution (Seth, '709).

DOUBLE PATENTING REJECTION:

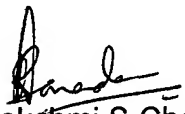
Applicants argue U.S. Patent No. 6,821,975 ('975) is directed to a compound and the composition claim only mentions diluents, excipients or a tablet or a capsule, as in the instant composition. However, applicants' argument is not persuasive because

instant claim also broadly recites the excipients, diluents etc., but does not state any specific compounds. Accordingly, the argument is moot.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakshmi S. Channavajjala whose telephone number is 571-272-0591. The examiner can normally be reached on 9.00 AM -6.30 PM

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K. Page can be reached on 571-272-0602. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Lakshmi S Channavajjala
Examiner
Art Unit 1615

September 18, 2005